(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 074 770**
A1

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: 82304650.3

(22) Date of filing: 03.09.82

(51) Int. Cl.^{3}: C 07 D 491/22
A 61 K 31/33
//(C07D491/22, 311/00, 221/00, 221/00, 209/00)

(30) Priority: 04.09.81 JP 138412/81

(43) Date of publication of application: 23.03.83 Bulletin 83/12

(84) Designated Contracting States: BE CH DE FR GB IT LI NL SE

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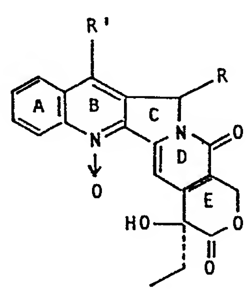
(54) Camptothecin-1-oxide derivatives, process for preparing same, formulations comprising said derivatives and said derivatives for use in producing an anti-tumour effect.

(57) New 5- and/or 7-substituted camptothecin-1-oxide derivatives possessing anti-tumor activity with slight toxicity are represented by the general formula:



(1)

wherein R is a hydrogen atom, an alkyl group, a hydroxyl group, an alkoxy group or an acyloxy group, and R' is a hydrogen atom, an alkyl group, an aralkyl group, a hydroxymethyl group, an acloxymethyl group or a carboxymethyl group, with the proviso that R and R' are not both hydrogen atoms. These 5- and/or 7-substituted camptothecin-1-oxide derivatives may be prepared by treating the corresponding 5- and/or 7-substituted camptothecins with a peroxidant as an N-oxidizing reagent.

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Croydon Printing Company Ltd.

TITLE: CAMPTOTHECIN-1-OXIDE DERIVATIVES, PROCESS FOR PREPARING SAME, FORMULATIONS COMPRISING SAID DERIVATIVES AND SAID DERIVATIVES FOR USE IN PRODUCING AN ANTI-TUMOR EFFECT.

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This invention relates to new camptothecin-1-oxide derivatives possessing anti-tumor activity (including carcino-static activity) and to processes for the preparation of such derivatives. More particularly, this invention relates to new 5- and/or 7-substituted camptothecin derivatives carrying an oxido group in the 1-position thereof and possessing anti-tumor activity, good absorbability and a low level of toxicity as well as processes for the preparation of such new camptothecin derivatives.

Camptothecin is a cytotoxic alkaloid isolated from leaves and barks of Camptotheca accuminata (Nyssaceae), a plant native to China, which has a pentacyclic structure consisting of a characteristic fused 5-ring system of quinoline (rings A and B), pyrroline (ring C), α-pyridone (ring D) and a six-membered lactone (ring E), and is distinguished by displaying a strong inhibitory activity toward biosynthesis of nucleic acids. In addition, camptothecin is a unique anti-tumor substance characterized by its rapid and reversible action and its lack of any cross-tolerance with the existing anti-tumor agents and by exhibiting a strong anti-tumor activity against experimentally transplanted carcinoma such as leukemia L-1210 in mice or Walker 256 tumor in rats. Although camptothecin is still regarded as one of the most potent substances possessing anti-tumor activity, the use of this compound itself for clinical treatments is significantly limited because of high toxicity.

Accordingly, a number of efforts have been made to reduce toxicity of camptothecin while maintaining its anti-tumor activity by converting camptothecin chemically into its derivatives. The chemical modifications so far reported are mainly about the rings D and/or E of camptothecin, but the results of such modifications revealed only failure in maintaining expected anti-tumor activity and poor improvement in toxicity [J. Med. Chem., 19 (1976), 675]. From the chemotherapeutic point of view, therefore, it is of importance that the chemical modifications of camptothecin should be restricted in the rings A, B and C without effecting any change in the rings D and E which are conceivably one of the essential structural elements for the expression of the above mentioned characteristic biological activities.

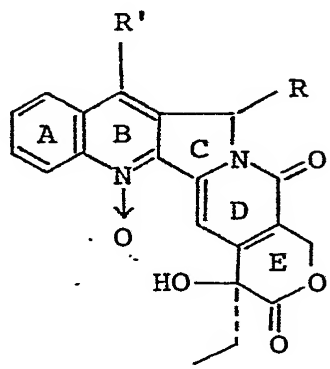
Except for a method for functionalizing the 12-position of camptothecin reported in 1976 which comprises a series of troublesome conversion and purification operations starting with nitration at 12-position [P. Pei-chuang et al., Hau Hsueh Hsueh Pao Vol. 33 (1975), 719; Chem. Abstr. 84 (1976) 115629p/, however,no success was reported until 1979 in connection with chemical functionalization of campothecin in a moiety involving the rings A, B, and C. This is probably attributable to the reason that camptothecin itself is only sparingly soluble in various organic solvents and that camptothecin possessing the nature of heterocyclic rings in its molecule is resistant to the so-called electrophilic reactions conventionally carried out on aromatic rings. In the present status, such obstacles strongly refuse chemical modifications of camptothecin contemplated on the desk for preparing new classes of derivatives thereof.

Under the above mentioned circumstances, the present inventors previously found together with co-workers processes for introducing (1) hydroxymethyl group into 7-position, (2) hydroxy group into 5-position and (3) an alkyl or aralkyl group into 7-position of camptothecin efficiently in a single step, and prepared a great number of new camptothecin derivatives possessing anti-tumor activity with slight toxicity from 5- and 7-substituted camptothecin obtained according to the above processes (Japanese Laid-open Patent Applns. Nos. Sho. 56-12391, 56-12392, 56-12393, 56-12394, 56-158786, 57-116075 and 57-116076; USSN 166,953 and 336,494; and DOS 30 26 172). However, the sorts of camptothecin derivatives prepared according to these processes are still limitative.

For further researches on the relation between the substituents in camptothecin derivatives and anti-tumor activity and/or toxicity, therefore, there is still a great demand in this art for developing further new classes of camptothecin derivatives possessing a low level of toxicity while maintaining the inherent anti-tumor activity by chemically modifying 5- and/or 7-substituted camptothecin in a single step without destroying the structure of the rings D and E in the camptothecin molecule.

This invention is based upon the discovery of certain 5- and/or 7-substituted camptothecin-1-oxide derivatives as a new class of camptothecin derivatives which can be prepared in a single step without permitting any attack on the rings D and E by treating a 5- and/or 7- substituted camptothecin derivative with a specific oxidizing agent. The new class of 5- and/or 7-substituted camptothecin-1-oxide derivatives have provided anti-tumor activity and extremely reduced toxicity.

In accordance with the present invention, there are provided new 5- and/or 7-substituted camptothecin-1-oxide derivatives of the general formula:



(I)

wherein R is a hydrogen atom, an alkyl group, a hydroxyl group, an alkoxy group or an acyloxy group, and R' is a hydrogen atom, an alkyl group, an aralkyl group, a hydroxymethyl group, an acyloxymethyl group or a carboxymethyl group, with the proviso that R and R' are not both hydrogen atoms.

In the above general formula (I), either one of the substituents R and R' is preferably a hydrogen atom. When R or R' stands for an alkyl group, it generally has 1-30 carbon atoms. In view of availability of alkylating reactants, the alkyl group has preferably 1-18 carbon atoms. Illustrative of the alkyl group are, for example, straight or branched chain alkyl groups with 1-30, preferably 1-18 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, n-heptyl, n-octyl, 2-ethylhexyl, n-nonyl, n-decyl, undecyl, dodecyl, myristyl, heptadecyl, octadecyl and eicosyl groups. When the alkyl groups are branched, the branched chains may be combined together to form a cycloalkyl group such as cyclopentyl, cyclohexyl or cycloheptyl group. When R stands for an alkoxy group, the alkyl moiety thereof

generally corresponds to the aforesaid alkyl group. Preferable examples of the alkoxy group are those derived from straight or branched chain lower alkyl groups with 1-8 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, tert-butoxy, n-pentyloxy, isopentyloxy, n-hexyloxy, n-heptyloxy, n-octyloxy and 2-ethylhexyloxy groups. When R stands for an acyloxy group, the alkyl moiety thereof generally corresponds to the aforesaid straight or branched chain alkyl group with 1-18 carbon atoms, such as formyloxy, acetyloxy, propionyloxy, n-butyryloxy, isobutyryloxy, valeryloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, decanoyloxy, undecanoyloxy, dodecanoyloxy, pentadecanoyloxy, hexadecanoyloxy and octadecanoyloxy groups. The acyl group in this case may be derived from aromatic carboxylic acids such as benzoic acid and nucleus-substituted benzoic acids; heterocyclic carboxylic acids such as nicotic acid; aralkylcarboxylic acids such as phenylacetic acid; and alkyl and aromatic sulfonic acids such as ethanesulfonic acid and nucleus-substituted or -unsubstituted benzenesulfonic acid. Preferable examples of the aralkyl group include benzyl, phenethyl, phenylpropyl and 1-naphthylmethyl groups. When R' is an acyloxymethyl group, the acyl moiety generally corresponds to the aforementioned acyl group. Preferable examples of the acyloxymethyl group include those having the acyl moiety with 1-8 carbon atoms, such as acetoxymethyl, propionyloxymethyl, butyryloxymethyl, valeryloxymethyl, hexanoyloxymethyl, benzoyloxymethyl, phenylacetoxymethyl, nicotinoyloxymethyl, ethanesulfonyloxymethyl and p-toluenesulfonyloxymethyl groups.

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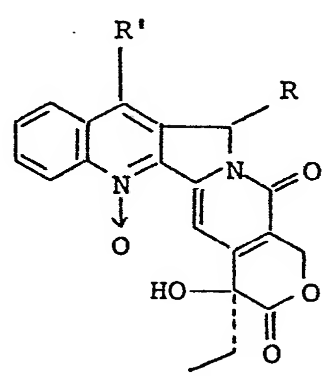
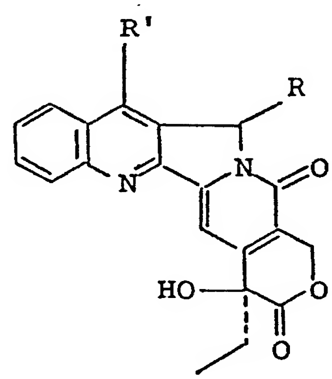
Illustrative of the new 5- and/or 7-substituted camptothecin-1-oxide derivatives of the present invention are 5-methylcamptothecin-1-oxide, 5-ethylcamptothecin-1-oxide, 5-propylcamptothecin-1-oxide, 5-butylcamptothecin-1-oxide, 5-octylcamptothecin-1-oxide, 5-hydroxycamptothecin-1-oxide, 5-methoxycamptothecin-1-oxide, 5-ethoxycamptothecin-1-oxide, 5-propoxycamptothecin-1-oxide, 5-butoxycamptothecin-1-oxide, 5-octyloxycamptothecin-1-oxide, 5-acetoxycamptothecin-1-oxide, 5-propionyloxycamptothecin-1-oxide, 5-hexanoyloxycamptothecin-1-oxide, 7-methylcamptothecin-1-oxide, 7-ethylcamptothecin-1-oxide, 7-propylcamptothecin-1-oxide, 7-butylcamptothecin-1-oxide, 7-hexylcamptothecin-1-oxide, 7-octylcamptothecin-1-oxide, 7-benzylcamptothecin-1-oxide, 7-phenylpropylcamptothecin-1-oxide, 7-hydroxymethylcamptothecin-1-oxide, 7-carboxymethylcamptothecin-1-oxide, 7-acetoxymethylcamptothecin-1-oxide, 7-propionyloxymethylcamptothecin-1-oxide, 7-butyryloxymethylcamptothecin-1-oxide, 7-hexanoyloxymethylcamptothecin-1-oxide, and 7-octanoyloxymethylcamptothecin-1-oxide.

In accordance with the present invention, there is also provided a process for the preparation of the new 5- and/or 7-substituted camptothecin-1-oxide derivatives of the general formula:



(I)

wherein R is a hydrogen atom, an alkyl group, a hydroxyl group, an alkoxy group or an acyloxy group, and R' is a hydrogen atom, an alkyl group, an aralkyl group, hydroxymethyl group, an acyloxymethyl group or a carboxymethyl group, characterized by treating a 5- and/or 7-substituted camptothecin derivative of the general formula:



(II)

wherein R and R' have the same meanings as given above, with a peroxidant in a liquid vehicle.

The 5- and/or 7-substituted camptothecin derivatives of the general formula (II) used as the starting material are known or can be prepared according to the known prior art processes.

The peroxidant utilizable in the process of this invention for N-oxidation of the ring B (pyridine ring) is selected from the group consisting of hydrogen peroxide, inorganic and organic peracids and salts thereof. Illustrative of the peroxidant are, for example, hydrogen peroxide, peracetic acid, perbenzoic acid, m-chloroperbenzoic acid and a persulfate. The use of hydrogen peroxide is preferable as a higher yield of the product is expected thereof. The procedure itself for the

N-oxidation wherein hydrogen peroxide is used as the peroxidant can be carried out in a manner similar to that described in Mosher et al., Org. Syn. 33, 79(1953), Ochiai et al., J. Pharm. Soc. Japan 71, 1385 (1951) or Boehelheide et al., J. Am. Chem. Soc. 76, 1286 (1954). This procedure can be applied as a new means for N-oxidation of camptothecin itself.

Preferable examples of the liquid vehicle include glacial acetic acid, an aqueous acetic acid solution, hydrocarbons such as benzene and hexane, chlorinated hydrocarbons such as chloroform and methylene chloride, and ethers such as dioxane.

In an embodiment using hydrogen peroxide as the peroxidant, the starting 5- and/or 7-substituted camptothecin derivative is suspended in a small amount of acetic acid or dissolved in a larger amount of acetic acid and then treated under agitation with hydrogen peroxide (usually, about 30% in concentration). The selection of a temperature range from 65°C to 70°C is adequate for this reaction. A theoretically needed quantity of hydrogen peroxide is one mol per mol of the starting camptothecin derivative, but the use of a larger excess of hydrogen peroxide (about 30 molar proportion) for the starting camptothecin derivative is preferable. Under such conditions, the N-oxidation of the starting compound is completed normally within 4 hours.

In another embodiment using a peracid as the peroxidant, the starting 5- and/or 7-substituted camptothecin derivative is treated, for example, with peracetic acid (usually, 40% in concentration) and a salt of acetic acid such as sodium acetate or with perbenzoic acid in benzene under conditions similar to those mentioned above. It is possible to use m-chloroperbenzoic

acid as the peroxidant in an organic liquid vehicle such as the above mentioned chlorinated hydrocarbons or ethers. It is also possible to use a persulfate as the peroxidant under the similar conditions. The N-oxidation reaction per se with these peracids and a persulfate is known and can be carried out, for example, according to the method as described in Herz et al., J. Am. Chem. Soc. 76, 4184 (1954) and Matsumura, J. Chem. Soc. 74, 446 (1953).

The resultant N-oxide product can be isolated in a highly pure form, for example, concentrating the reaction mixture under reduced pressure to a volume of about 1/5 - 1/10, diluting the concentrate with a large excess of ice water, collecting the resultant N-oxide precipitated as needle crystals by filtration, and drying the crystals under subatmospheric pressure. The products thus obtained can be used as such without further purification as active ingredients for medicaments or as intermediate products for preparing other useful products.

The present invention is of particular significance in developing a new class of camptothecin derivatives useful as anti-tumor agents possessing anti-tumor activity with slight toxicity and as intermediate products for preparing other useful products as well as a process for preparing these new camptothecin derivatives in a simple industrially advantageous operation.

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The invention includes a new camptothecin derivative as defined above and prepared by the process of the invention for use in producing an anti-tumor effect in man or any other animal.

The invention further provides a pharmaceutical or veterinary formulation comprising a new camptothecin derivative as defined above or prepared by the process of the invention, in either case formulated for pharmaceutical or veterinary use, respectively. The formulations of the invention can be in unit dosage form in accordance with normal practice and/or may comprise one or more acceptable diluents, carriers or excipients.

The present invention will now be illustrated in more detail by way of Examples. In these Examples, percentages are by weight unless otherwise indicated.

Example 1 (Preparation of camptothecin-1-oxide)

Camptothecin (1.04 g, 3 m-mol) is suspended in acetic acid (100 ml). To this suspension is added 30% hydrogen peroxide (15 ml), and the mixture is stirred for 3 hours at 60-70°C. The resultant reaction mixture is concentrated under reduced pressure to a volume of about 35 ml and the concentrate was then poured into ice water (500 ml). The precipitated yellowish orange needle crystals are collected by filtration, washed with water and then with methanol and dried under reduced pressure whereby 866 mg (yield: 90.6%) of camptothecin-1-oxide is obtained. M.P. 254°C (dec.)

Example 2 (Preparation of 5-methylcamptothecin-1-oxide)

5-Methylcamptothecin (362 mg, 1 m-mol) is dissolved in acetic acid (25 ml). To this solution is added 30% Hydrogen peroxide (2.5 ml, 0.0245 mol), and the mixture is warmed for 3 hours at 65-70°C. The reaction mixture is concentrated under reduced pressure to a volume of about one fifth and diluted with ice water (250 ml). The precipitated yellowish orange needle crystals are collected by filtration and dried at 60°C for 6 hours under reduced pressure whereby 234 mg (yield: 62.0%) of 5-methylcamptothecin-1-oxide is obtained. M.P. 226°C- (dec.)
MS : m/e 378 $[M^+]$ ($C_{21}H_{18}N_2O_5$ =378)

Example 3 (Preparation of 5-methoxycamptothecin-1-oxide)

5-Methoxycamptothecin (190 mg, 0.5 m-mol) is dissolved in acetic acid (15 ml). To this solution is added 30% hydrogen peroxide (1.25 ml , 0.0125 mol), and the mixture is stirred for 3 hours at 65-70°C. The reaction mixture is concentrated under reduced pressure to a volume of about one fourth and diluted with ice water (200 ml). The precipitated yellowish orange needle crystals are collected by filtration and then dried under reduced

pressure for 6 hours at 60°C whereby 145 mg (yield: 73.6 %) of 5-methoxycamptothecin-1-oxide is obtained. M.P. 208°C- (dec.)

NMR (in $CDCl_3$) : 1.03 (3H, t, J=7 Hz), 1.92 (2H, q, J=7 Hz), 3.51, 3.66 (1.5H x 2, s, s), 5.30 (1H, d, J=16 Hz), 5.59 (1H, d, J=16 Hz), 6.73, 6.85 (0.5H x 2, s, s), 7.72-8.01 (4H, m), 8.24 (1H, s), 8.76 (1H, m)

MS : m/e 394 $[M^+]$ ($C_{21}H_{18}N_2O_6$ =394)

Example 4 (Preparation of 7-ethylcamptothecin-1-oxide)

7-Ethylcamptothecin (1.00 g, 2.65 m-mol) is dissolved in acetic acid (300 ml). To this solution is added 30% hydrogen peroxide (7.5 ml, 0.0736 mol), and the mixture is stirred for 3 hours at 65-70°C. The reaction mixture is concentrated under reduced pressure to a volume of about one fourth and diluted with ice water (500 ml). The precipitated yellowish orange needle crystals are collected by filtration and dried for 6 hours at 60°C under reduced pressure whereby 808 mg (yield: 77.7%) of 7-ethylcamptothecin-1-oxide is obtained. M.P. 255°C- (dec.)

NMR (in DMSO-d_6) : 0.87 (3H, t, J=7 Hz), 1.28 (3H, t, J=7 Hz), 1.84 (2H, q, J=7 Hz), 3.10 (2H, q, J=7 Hz), 5.26 (2H, s), 5.36 (2H, s), 6.24 (1H, s, D_2O-exchangeable), 7.80 (3H, m), 8.10 (1H, s), 8.35 (1H, m)

MS : m/e 392 $[M^+]$ ($C_{22}H_{20}N_2O_5$ = 392)

Example 5 (Preparation of 7-propylcamptothecin-1-oxide)

7-Propylcamptothecin (390 mg, 1 m-mol) is dissolved in acetic acid (55 ml). To this solution is added 30% hydrogen peroxide (3 ml, 0.0294 mol), and the mixture is stirred for 4 hours at 65-70°C. The reaction mixture is concentrated under reduced pressure to a volume of about 10 ml and diluted with ice water (250 ml). The precipitated yellowish orange needle

crystals are collected by filtration and dried for 6 hours at 60°C under reduced pressure whereby 278 mg (yield: 68.4%) of 7-propylcamptothecin-1-oxide is obtained. M.P. 238°C- (dec.)

MS : m/e 406 $[M^+]$ ($C_{23}H_{22}N_2O_5$ =406)

Example 6 (Preparation of 7-benzylcamptothecin-1-oxide)

7-Benzylcamptothecin (250 mg, 0.570 m-mol) is dissolved in acetic acid (50 ml). To this solution is added 30% hydrogen peroxide (2 ml, 0.0196 mol), and the mixture is stirred for 3 hours at 65-70°C. The reaction mixture is concentrated under reduced pressure to a volume of about 10 ml and then diluted with ice water (250 ml). The precipitated yellowish orange needle crystals are collected by filtration and dried for 6 hours at 60°C under reduced pressure whereby 164 mg (yield: 63.5%) of 7-benzylcamptothecin-1-oxide is obtained. M.P. 220°C- (dec.)

NMR (in $CDCl_3$) : 1.09 (3H, t, J=7.5 Hz), 1.87 (2H, q, J=7.5 Hz), 4.48 (2H, s), 5.16 (2H, s), 5.20 (1H, d, J=16 Hz), 5.64 (1H, s, J=16 Hz), 7.05-8.12 (8H, m), 8.32 (1H, s), 8.80 (1H, m)

MS : m/e 454 $[M^+]$ ($C_{27}H_{22}N_2O_5$ =454)

Example 7 (Preparation of 7-acetoxymethylcamptothecin-1-oxide)

7-Acetoxymethylcamptothecin (1.0 g, 2.38 m-mol) is dissolved in acetic acid (150 ml). To this solution is added 30% hydrogen peroxide (10 ml, 0.0981 mol), and the mixture is stirred for 3.5 hours at 65-70°C. The reaction mixture is concentrated under reduced pressure to a volume of about 50 ml, diluted with ice water (350 ml) and extracted with chloroform (300 ml x 3). The chloroform phase is washed with a 7% aqueous solution of sodium hydrogen carbonate, dried over magnesium sulfate and dried until dryness under reduced pressure. The residue is purified by reprecipitation with chloroform-n-hexane whereby

679 mg (yield: 65.9%) of 7-acetoxymethylcamptothecin-1-oxide is obtained as yellow needle crystals. M.P. 250°C- (dec.)

NMR (in DMSO-d_6) : 0.87 (3H, t, J=7 Hz), 1.83 (2H, q, J=7 Hz), 2.05 (3H, s), 5.42 (4H, br s), 5.61 (2H, s), 6.42 (1H, s, D_2O-exchangeable), 7.80 (2H, m), 7.91 (1H, s), 8.20 (1H, m), 8.63 (1H, m)

MS : m/e 436 [M^+] ($C_{23}H_{20}N_2O_7$ =436)

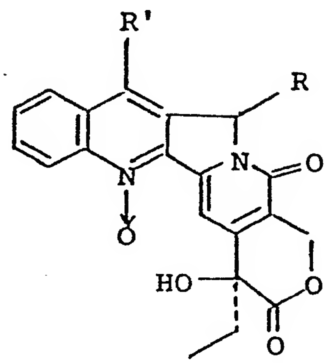
Example 8 (Preparation of 7-hydroxymethylcamptothecin-1-oxide)

7-Hydroxymethylcamptothecin (300 mg, 0.794 m-mol) is suspended in glacial acetic acid (70 ml). To this suspension is added 30% hydrogen peroxide (30 ml), and the mixture is stirred for one hour at 70-80°C. 30% Hydrogen peroxide (20 ml) is added and the mixture is further stirred for 1.5 hours at 70-80°C. The reaction mixture is concentrated under reduced pressure to a volume of 40 ml. Ice water (60 ml) is added to the concentrate and the mixture is allowed to stand for 12 hours. The precipitated yellow crystals are collected by filtration and dried under reduced pressure whereby 142 mg (yield: 45.4%) of the title compound is obtained as yellow needle crystals. M.P. 255-260°C (dec.)

IR $\nu_{max}^{KBr}cm^{-1}$: 3400, 2940, 1755, 1650, 1600, 1460, 1160, 1100, 765

CLAIMS:

1. A 5- and/or 7-substituted camptothecin-1-oxide derivative of the formula:



(I)

wherein R is a hydrogen atom, an alkyl group, a hydroxyl group, an alkoxy group or an acyloxy group, and R' is a hydrogen atom, an alkyl group, an aralkyl group, a hydroxymethyl group, an acyloxymethyl group or a carboxymethyl group, with the proviso that R and R' are not both hydrogen atoms.

2. 5-Alkylcamptothecin-1-oxide.

3. 5-Alkoxycamptothecin-1-oxide.

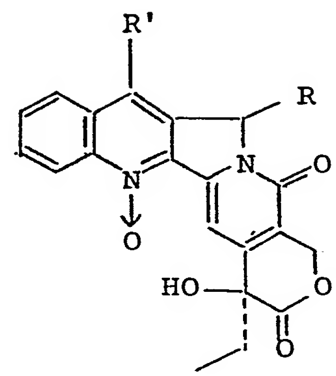
4. 7-Alkylcamptothecin-1-oxide.

5. 7-Aralkylcamptothecin-1-oxide.

6. 7-Acyloxymethylcamptothecin-1-oxide.

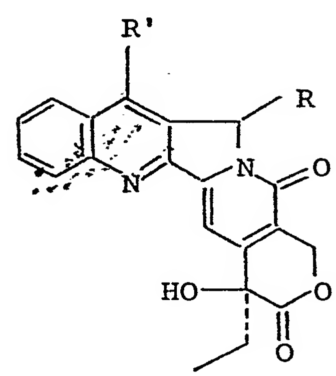
7. 7-Hydroxymethylcamptothecin-1-oxide.

8. A process for the preparation of 5- and/or 7-substituted camptothecin-1-oxide derivatives of the general formula:



(I)

wherein R .. is · a hydrogen atom, an alkyl group, a hydroxyl group, an alkoxy group or an acyloxy group and R' is · a hydrogen atom, an alkyl group, an aralkyl group, a hydroxymethyl group, an acyloxymethyl group or a carboxymethyl group, characterized by treating a 5- and/or 7-substituted camptothecin derivative of the general formula:



(II)

wherein R and R' have the same meanings as given above, with a peroxidant in a liquid vehicle.

9. A process according to claim 8, wherein the peroxidant is hydrogen peroxide, an inorganic or organic peracid or a salt thereof.

10. A process according to claim 8 or claim 9, wherein the liquid vehicle is acetic acid, a hydrocarbon, a chlorinated hydrocarbon or an ether.

11. A process according to any one of claims 8 to 10, wherein the treatment is carried out within a temperature range from 55°C to 90°C.

12. A process according to any one of claims 8 to 11, wherein the peroxidant is used in an amount which is in excess relative to the amount of the 5-and/or 7- substituted camptothecin derivative.

13. A pharmaceutical or veterinary formulation comprising a compound according to any one of claims 1 to 7, or a 5- or 7-substituted camptothecin-1-oxide derivative which has been prepared by a process according to any one of claims 8 to 12, in either case formulated for pharmaceutical or veterinary use, respectively.

14. A compound as defined in any one of claims 1 to 7 or a 5- or 7-substituted camptothecin-1-oxide derivative which has been prepared by a process according to any one of claims 8 to 12 for use in producing an anti-tumor effect in man or any other animal.

European Patent Office

0074770

EUROPEAN SEARCH REPORT

Application number

EP 82 30 4650

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
D,A	--- DE-A-3 026 172 (K.K.YAKULT HONSHA) *Claims* -----	1	C 07 D 491/22 A 61 K 31/33 // (C 07 D 491/22 C 07 D 311/00 C 07 D 221/00 C 07 D 221/00 C 07 D 209/00)
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			C 07 D 491/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	09-12-1982	VAN BIJLEN H.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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